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Epidemiology of AIDS-related malignancies: An international perspective

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The sudden appearance of Kaposi's sarcoma (KS) in 1981 [1] [2] and, shortly thereafter, the appearance of high-grade non-Hodgkin's lymphoma (NHL) [3] [4] in a handful of young homosexual men who otherwise seemed in good health signaled the start of a new epidemic, now known as AIDS [5] [6] . The profound immunosuppression found in people with AIDS raised concerns that an epidemic of associated cancers might occur [7] . Two decades later, only the relative risks (RRs) for KS and some NHL subtypes are recognized to be markedly elevated in people with AIDS [8] . In addition to these tumors, cervical cancer is designated as an AIDS-defining illness in women who are HIV infected [9] , although it is not increased definitively with AIDS [10] . Reassuringly, the RRs for the most common epithelial cancers in the general population—lung, breast, colon/rectum, stomach, liver, and prostate cancer [130] —are not increased substantially in people with AIDS [11] Table 1 .

Table 1. Relative risk for selected cancers 4 to 27 months after AIDS onset, UnitedStates AIDS/Cancer Match Registry Study

Site	Relative risk (range)
AIDS-defining cancers	
Karposi's sarcoma	177.7 (173.2–182.3)

Non-Hodgkin's lymphoma	72.8 (70.4–75.3)
Cervical cancer	5.2 (3.8–6.9)
Non–AIDS-defining cancers	
Hodgkin's lymphoma	6.7 (5.3–8.3)
Mixed cellularity	9.1 (5.8–13.5)
Lymphocyte depleted	10.7 (2.2–31.2)
Lymphocyte predominant	1.3 (0.0–7.2)
Nodular sclerosis	2.8 (1.7–4.5)
Respiratory	2.6 (2.3–2.9)
Lung cancer	2.8 (2.4–3.1)
Digestive	1.6 (1.3–1.8)
Anus, not specified squamous cell carcinoma	14.3 (5.7–29.5)
Anus, squamous cell carcinoma	22.8 (16.9–30.0)
Lip, oral cavity, and pharynx	2.3 (1.8–2.9)
Lip	5.1 (2.0–10.4)
Liver/intrahepatic ducts	3.1 (2.0–4.6)
Male genital organs	0.8 (0.6–1.0)
Penis	5.1 (1.7–11.9)
Prostate	0.5 (0.4–0.7)
Testicular nonseminoma	1.0 (1.1–2.6)
Testicular seminoma	1.8 (1.1–2.6)
Female genital organs	1.5 (0.8–2.5)
Vulva/vagina	10.5 (4.5–20.8)
Corpus uteri	0.8 (0.2–2.4)
Ovary	0.5 (0.1–1.6)
Brain and central nervous system	3.6 (2.7–4.7)
Eye	3.1 (0.8–8.0)
Soft tissue	3.6 (2.3–5.3)

Frisch et al [11].

This article reviews the trends in AIDS-associated cancers, before and after the introduction of highly active antiretroviral therapy (HAART), and highlights the impact of the epidemic on cancer risk in Africa, where the majority of people with AIDS live.

KS

The earliest reference to KS in the medical literature is from Moritz Kaposi in 1872. Originally known as Moritz Kohn, he adopted the name of his birthplace Kaposivar on the Kapos River. One hundred and

thirty years after he described it, KS continues to intrigue researchers, particularly because it was associated with the initial description of AIDS in 1981 [12] .

Before the AIDS epidemic, KS was known to occur in three epidemiologic forms [13] . Classic KS, the syndrome described by Moritz Kaposi, is characterized by plaques or nodules erupting on the feet and hands, rarely invading viscera or causing death. This form is found most frequently in elderly men (70 years or older, male to female ratio > 3 to 1) of the Mediterranean and Eastern Europe [13] [14] [15] . Migrants from high incidence areas (eg, Italy, Poland, Russia, and Eastern Europe) to Western Europe or North America seem to carry their predisposition for KS [16] [17] . The disease is relatively rare in the United Kingdom, Scandinavia, and other parts of Northern and Western Europe.

KS in Africa was first reported in Nigeria in the early 1900s [18] , but numerous reports subsequently established the highest incidence to occur in equatorial Africa [19] . This form, referred to as endemic KS, is similar to classic KS in its male predominance among adults (male to female ratio ≥ 10 to 1), but differs in showing a bimodal age distribution, a larger mode occurring at a median age of 30 to 50 years, and a smaller mode at 5 to 9 years [19] [20] . Clinically, lesions typically erupt on the feet and hands, beginning as plaques and progressing to nodules that can coalesce to become florid. Endemic KS also can erupt elsewhere on the body, however, and visceral involvement is common. Children with KS frequently have lesions in lymph nodes and in the conjunctiva or palpebra, but rarely on the skin (Fig. 1) . In children, progression to death typically occurs within months [19] . The incidence of KS in Africa varies, being highest in countries around the Nile-Congo watershed, which accounted for 3% to 10% of all cancers diagnosed in the pre-AIDS era [21] .

Fig. 1. Clinical manifestations of pediatric KS in a child seen at the Uganda Cancer Institute. Note the enlarged axillary and inguinal lymph nodes and facial edema.

The third form of KS appeared following advances in transplant medicine, with the introduction of immunosuppressive regimens used to prevent graft rejection; thereafter, posttransplant patients developed disseminated KS at an alarming rate [22] [23] . This form, referred to as posttransplant or iatrogenic KS, often resolves when immunosuppressive therapy is stopped, calling attention to immune deficiency as an etiologic cofactor [23] [24] .

In 1981, the appearance of KS in otherwise healthy young men provided an early signal of a new disease of immune suppression. These cases represented the fourth and most recent epidemiologic manifestation of KS—that is, epidemic or AIDS-associated KS [1] . Because KS was rare in the United States before the AIDS epidemic, the epidemiology of KS in the United States predominantly reflects the epidemiology of AIDS-related KS [25] . The incidence of KS in white men was 0.3 per 100,000 before the AIDS epidemic (1973–1978), but rose to as high as 8.9 between 1989 and 1991, the years in which the incidence of KS was highest. AIDS-related KS occurs at a relatively young median age; less than 11% of people with KS were aged 20 to 54 years in the period from 1973 to 1978, but the proportion in this age group rose to 90% after the onset of the AIDS epidemic.

The risk of AIDS-related KS differs by HIV exposure category and has changed over time. Compared with the general population, the RR for KS in people who were diagnosed with AIDS was elevated 106,000-fold in homosexual men and 13,000-fold in people exposed to HIV through injection drug use or heterosexual activity, based on the national AIDS/Cancer Match Registry Study data through 1990

[26] . About 40% to 50% of homosexual men with AIDS developed KS at the onset of the epidemic, but this proportion fell to less than 15% in the late 1980s. In contrast, only 10% of injection drug users, 4% of people with hemophilia, and 3% of children with AIDS presented with KS among the AIDS cases reported to the Centers for Diseases Control and Prevention through March 1989[27] . In homosexual men, the risk for KS was variously associated with reported number of homosexual partners, receptive penile anal or insertive oral–anal intercourse, or sexually transmitted infections [27] . These associations prompted a search for a sexually transmitted cofactor [27] , and led to the discovery in 1994 of a novel herpesvirus, now called human herpesvirus 8 (HHV-8, also called KS-associated herpesvirus) [28] .

Histologically, all epidemiologic forms of KS appear the same, characterized by vascular clefts and spindle cells, the presumed tumor cells [29] . KS behaves like an inflammatory lesion in its early phases, with much vascular reaction and scanty spindle cells; however, the proportion of spindle cells increases as the lesions mature [30] . No consistent chromosomal or genetic abnormalities have been demonstrated in KS spindle cells, and it is not certain whether KS lesions are derived from a single clone. Reports of noncontignous lesions that are monoclonal supports metastatic spread [31] , but not all studies agree [32] . KS may start as a polyclonal proliferation from which clonal outgrowth occurs when cells lose their responsiveness to normal cellular growth controls.

HHV-8 and KS

Accumulating evidence indicates that HHV-8 is necessary, but not sufficient, for the development of KS; other factors also contribute [33] . HHV-8 can be detected by the polymerase chain reaction in KS tissue from all epidemiologic forms, but not in control tumors or normal skin biopsies [34] . Furthermore, the detection of HHV-8 DNA in peripheral blood predicts risk for developing KS in homosexual men [35] . The risk for developing KS increases with immunosuppression, as measured by declining CD4 cell counts and duration of time since HIV infection [8] [36] . Moreover, the risk for developing KS correlates well with HHV-8 viral load, and KS and HHV-8 are inversely correlated with immune competence [35] . Although absolute HHV-8 prevalence is uncertain because of the inadequacy of current assays, the relative prevalence of HHV-8 seropositivity tends to be higher in those regions or populations in which the incidence of KS also is high [13] . Contrary to this generalization are reports of a high prevalence of lytic antibody in adolescents in Egypt (56%)—an area in which KS is rare—but a low prevalence of latent antibody in Cameroon (8%) and in Uganda (19%–26%), despite these countries having a clearly higher incidence of KS [37] . Furthermore, no differences were observed in HHV-8 antibody seropositivity between Uganda and Zambia, although their incidence of KS differs by approximately twofold [37] . Similarly, a high prevalence of HHV-8 seropositivity is reported in the Gambia [38] and Botswana [39] , although these countries have not been reported to have a high incidence of KS. These inconsistencies in HHV-8 seropositivity may be due to variation in the distribution of unknown cofactors or imperfect assay performance.

The modes of HHV-8 transmission are poorly understood. Early studies in homosexual men implicated transmission through sexual contact, but in recent studies [40] the detection of HHV-8 DNA more readily in saliva than in genital secretions suggests an important role for salivary transmission. In HHV-8 endemic areas such as Africa [41] and Israel [42] , transmission seems to occur mainly within families, perhaps through exposure to HHV-8 in saliva. HHV-8 seropositivity in children is associated with having antibodies to hepatitis B [43] , a virus transmitted from person to person, which suggests similar transmission of HHV-8. A horizontal pattern of infection also is suggested by the linear increase with age in HHV-8 seropositivity in children, as is observed with other herpes viruses [43] [44] [45] . Although HHV-8 DNA can be detected in peripheral blood mononuclear cells [46] [47] , blood-borne transmission has not been shown definitively [48] . Cannon et al [49] recently reported that women who injected illicit drugs daily were 3.2-fold more likely to have HHV-8 antibodies than were women who had never injected drugs. Similarly, Goedert et al [50] found that women who reported injection drug use and also

had antibodies to hepatitis C virus were 3.5-fold more likely to be HHV-8 seropositive than were women without these factors. Moreover, two studies that directly examined the risk of HHV-8 transmission to blood transfusion recipients in the United States and Jamaica did not observe seroconversions in recipients, but also were unable to exclude a transmission risk as large as 11% per seropositive unit [48] [51] . Whether blood-borne transmission occurs remains an important question, particularly for those populations in which HHV-8 is common.

How HHV-8 causes KS is actively under investigation. The HHV-8 genome has a high degree of homology with some cellular genes that are active in cell cycle regulation. These “pirated” genes include viral cyclins, antiapoptotic factors (eg, viral FLICE inhibitory protein, vBCL-2), viral cytokines and chemokines (eg, viral interleukin 6 [vIL-6], viral macrophage inflammatory proteins), and several transactivating proteins that also are present in other herpesviruses [30] [52] . These genes can disrupt mitosis, interrupt apoptosis, increase angiogenesis, and block presentation of antigenic epitopes, which may contribute variably to the pathogenesis of KS [52] . Because only a fraction of HHV-8–infected people develop KS, other factors also must be important. In HIV-infected people, HIV-tat protein may act synergistically with declining immune competence to increase risk for KS in people with AIDS [53] .

It is hoped that studies using new technologies, such as gene expression microarray techniques, will reveal host–virus gene interactions that are important in the pathogenesis of KS [54] , and help to identify molecular targets for treatment or prevention [55] . For example, DNA microarray studies of HHV-8–infected dermal endothelial cells demonstrated high levels of c-Kit expression in spindle cells presumably induced by HHV-8 infection [55] . If shown to be relevant in vivo, these results might prompt trials with c-Kit inhibitors such as imatinib mesylate, which is used for the treatment of chronic myeloid leukemia [56] .

Trends in KS in the era of HAART

After increasing rapidly during the AIDS epidemic, the incidence of KS began to decline even before the introduction of HAART. In 1987, the incidence of KS in white men was highest in areas with a high prevalence of AIDS, peaking at 32.1 (per 100,000) in San Francisco, 8.4 in Atlanta, and 8.4 in Hawaii. By 1998, KS incidence fell by more than 90% in these regions to 2.8, 1.0, and 0.7, respectively [25] . The fall in KS incidence may be related to a fall in the incidence of new HIV infections among homosexual men, the population at greatest risk for AIDS-related KS. In addition, HIV-infected homosexual men may have changed their behavior because of the AIDS epidemic, and coincidentally reduced their risk for HHV-8 infection and for developing KS. More recently, the introduction of progressively more efficacious antiretroviral therapies for HIV has slowed progression to AIDS and reduced the risk for developing KS in people who are HIV infected. Although not proven easily, the pool of homosexual men who are susceptible to HHV-8 infection or to KS also may have diminished.

NHL

NHL is the second most common tumor in people with AIDS. Tumors of high clinical grade (with the exception of lymphoblastic lymphoma) are designated as AIDS–defining, and include small noncleaved lymphoma (Burkitt's or non-Burkitt's), large cell lymphoma, immunoblastic lymphoma, and primary central nervous system (PCNS) lymphoma [57] . NHL previously accounted for about 3% of AIDS-defining clinical conditions [8] , but this proportion has declined, in part because of a surge in reportable AIDS cases that occurred when the AIDS definition was changed to include a low CD4 T-cell count [58] . Based on data from the AIDS/Cancer Match Registry, the RR is highest for immunoblastic lymphoma (RR = 627 versus 348 for other high-grade NHL), intermediate for intermediate-grade NHL (RR = 113),

and much lower for low-grade NHL (RR = 14) [8] [131] . Unlike KS, appreciable background rates of NHL in the general population somewhat obscure trends in AIDS-related NHL in cancer registry data; however, changes in NHL rates for those regions with a large population of people with AIDS and histologies and sites that are associated with AIDS closely reflect trends in AIDS-related NHL. In cancer data recorded from 11 regions in the United States in the Surveillance Epidemiology and End Results (SEER) Program, NHL incidence (per 100,000) in white men rose gradually from 10.4 in 1973 to 14.5 in 1983 before the onset of the AIDS epidemic, then increased more rapidly to peak at 21.1 in 1995 [25] . NHL incidence was highest in San Francisco, Hawaii, Atlanta, and Seattle (regions with large populations of people with AIDS) and lowest in Utah and Iowa (regions in which the prevalence of AIDS is much lower). With regard to site-specific rates, PCNS lymphoma incidence rose 65-fold from 0.02 in 1973 to a peak of 1.3 in 1995, with the highest rates in San Francisco.

The risk factors for AIDS-associated NHL are poorly understood, but the absolute risk increases with age and is higher in men and in whites [59] . In people with AIDS, the RR for NHL increases with duration of HIV infection and with decline in immune competence, and is stronger for immunoblastic, diffuse large B cell (DLBC), and PCNS lymphoma than for Burkitt's lymphoma. Epstein-Barr virus (EBV) is detected in approximately 50% of all AIDS-related NHL, including nearly 100% of PCNS lymphoma, 50% to 70% of DLBC lymphoma, and 30% of Burkitt's lymphoma [60] . EBV-infected lymphocytes express EBV latent membrane protein (LMP-1), a viral analog of the family of tumor necrosis factor (TNF) receptors in human cells that may contribute to NHL pathogenesis by interfering with cell-cycle control. Because some NHLs are EBV negative, an additional contributory mechanism may be the chronic antigenic stimulation that is common in people with AIDS. For example, AIDS patients who have elevated circulating serum cytokines such as IL-6 or elevated serum gamma globulin (markers of B-cell stimulation) have an excess risk for NHL [61] . Lymphocytes with sporadic mutations in *bcl-6* or *c-myc* genes may be positively selected, providing a pathway for some of the EBV-negative NHLs [60] . A polymorphism in the stromal cell-derived factor 1 gene that is correlated with elevated levels of this chemokine was associated with a twofold and fourfold increase in risk for NHL among those who were heterozygous and homozygous, respectively [62] . The relationship of genetic polymorphisms in cytokine genes to NHL risk needs to be clarified in future studies.

Primary effusion lymphoma (PEL) is a rare lymphoma with tropism for serous body cavities (pleural, peritoneal, or pericardial cavities), although dissemination to or initial manifestation in viscera can occur [63] . PELs typically express high HHV-8 copy numbers (60–100 per cell), are CD45 receptor-positive, lack *c-myc* oncogene rearrangements, have indeterminate immunophenotype, and frequently are co-infected with EBV. The proportion of NHL due to PEL is not known. The introduction of a morphologic code for PEL in the *International Classification of Diseases of Oncology, Third Edition* [132] is expected to facilitate future epidemiologic studies of PEL [64] . Based on clinical series, risk factors for PEL include homosexual sexual contacts, a prior diagnosis of KS, and multicentric Castleman disease, all of which can be explained as surrogate markers for HHV-8 infection.

Trends of NHL in relation to HAART

The introduction of HAART regimens in 1996 radically changed the clinical spectrum of HIV infection and AIDS. The incidence of opportunistic infections, KS, and AIDS-related mortality fell precipitously, but the impact of HAART on the incidence of NHL is less clear [65] [66] . The incidence of systemic NHL in the Multicenter AIDS Cohort Study [67] continued to rise by 0.8% per year in the period from 1996 to 1997, as HAART became widely available. Similarly, although HAART was associated with striking reductions in incidence of KS and of all opportunistic illnesses combined in the Swiss HIV cohort, no significant reductions were observed in the incidence of systemic NHL (Fig. 2) [Not Available] [68] . Data from the AIDS Clinical Trial Group trials [69] also did not indicate a significant decline in systemic NHL incidence (0.6% in the early 1990s and 0.4% in 1996–1997). These studies may have been

underpowered to show significant declines in systemic NHL because of relatively short follow-up or small numbers of cases.

Fig. 2. **(Figure not Available)** Incidence per 100 person years (with 95% CIs) of KS, NHL, and all opportunistic illnesses combined in Swiss HIV Cohort Study participants before and after the introduction of HAART. Incidences given at the start represent the 6 months before initiation of HAART; percentages (with 95% CI) in each graph indicate the reduction in incidence per month and correspond to the slopes of the log linear regression lines. (*Adapted from* Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA 1999;282:2222–6; with permission.)

Some studies have shown reductions in NHL, however. In the French Hospital Database [70] , the incidence of systemic NHL among HIV-seropositive subjects fell from 0.86% per year in the period from 1993 to 1994 to 0.43% in the period from 1997 to 1998; the incidence of PCNS lymphoma also fell significantly, from 0.28% to 0.097%. The higher mean CD4 lymphocyte count among subjects during the HAART period than before the HAART period (191 versus 63 cells per cubic millimeter) may explain, in part, these results. Indeed, within specific CD4-count strata, changes in NHL incidence rates were not significant [70] . An analysis of 8471 HIV seropositive patients over 26,764 person years in the EuroSIDA study [71] showed a highly significant reduction in annual NHL incidence, from 1.29% in the pre-HAART period to 0.57% in the post-HAART period. Reductions in incidence were most striking for immunoblastic (0.5% to 0.1%), PCNS (0.83% to 0.04%), and Burkitt's (0.18% to 0.03%) lymphoma [71] .

Recent analysis of data from the SEER Program [25] suggests that the incidence of AIDS-related NHL may be declining. The incidence of systemic NHL in San Francisco fell from a broad peak of 31.4 per 100,000 in 1996 to 21.6 in 1998. Decreases also occurred in AIDS-related NHL histologies and sites, specifically in immunoblastic, Burkitt's, and PCNS lymphoma. In contrast, the incidence of non–AIDS-associated NHL types, such as small cell lymphocytic and follicular lymphomas, continued to rise, consistent with the long-term increase in incidence of NHL among people without AIDS (Fig. 3) [25] .

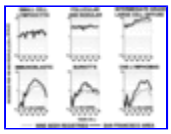

Fig. 3. Age-standardized incidence of selected NHL types among white men, SEER registries and San Francisco registry only, 1978 through 1998 [25] . Years with no cases were set arbitrarily at 0.12 cases on the log scale. CNS, central nervous system.

An international meta-analysis [72] indicated that NHL incidence in HIV-infected people fell from 0.62% per year in the pre-HAART era (1992–1996) to 0.36% when HAART regimens were available widely (1996–1999). In this analysis, significant reductions were observed for immunoblastic lymphoma (0.3% to 0.17%) and primary PCNS lymphoma (0.17% to 0.07%), but not for Burkitt's lymphoma (0.03% to 0.04%) [72] . Individually, all but one of the studies included in the meta-analysis found reductions in NHL incidence, and only one study found an elevated risk. Because HAART has been available only for a few years, longer follow-up may be needed to observe the full impact of HAART on the incidence of AIDS-related systemic NHL, especially as HIV-infected people survive longer with milder degrees of immune compromise.

The prognosis of AIDS-related NHL has improved in the era of HAART [70] [73] , in part due to higher mean CD4 counts at NHL diagnosis, which has allowed patients to better tolerate chemotherapy [66] [70] . HAART was associated with an 84% reduction in mortality after NHL diagnosis in a recent analysis of the Multicenter AIDS Cohort Study [73] . In this study [73] , improvement in survival occurred in patients who had started HAART before their NHL diagnosis and in those who started HAART after their NHL

diagnosis. The results parallel reports from clinical case studies [74] [75] in which dramatic improvements in survival and regression of PCNS lymphoma were reported soon after the introduction of HAART.

Hodgkin's lymphoma

Although not designated as an AIDS-defining cancer, Hodgkin's lymphoma incidence is elevated in people with AIDS. The RR of Hodgkin's lymphoma increases with time since HIV infection and with declining CD4 lymphocyte counts [11] [76] [77] . Although misclassification of NHL as Hodgkin's lymphoma could cause a spurious association between Hodgkin's lymphoma and AIDS, this explanation was not supported by a study [78] that included a review of histology. In the most recent AIDS/Cancer Match Registry Study [11] , the RR increased significantly from 2.6 per 100,000 in the period from 5 years or more before AIDS onset, to 9.8 in the period from 24 to 7 months before AIDS onset and 6.7 in the period from 4 to 27 months after AIDS onset. The tumors in HIV-positive patients are most frequently of mixed cellularity histology (54%), followed by nodular sclerosis (34%), lymphocyte depleted (9%), and lymphocyte predominant (3%). The corresponding RRs for these histologic subtypes are 9.1, 2.8, 10.7, and 1.3, respectively. Significantly, the subtypes with the highest RRs are those of “classic” Hodgkin's lymphoma, for which the tumor cells are EBV positive in approximately 50% of cases [79] ; more than 80% of the tumors in people with AIDS have detectable EBV. Reed-Sternberg cells of these cases express the EBV-encoded LMP-1, which functions as a constitutively activated TNF receptorlike molecule. LMP-1 activation of physiologically relevant signaling pathways may be an important mechanism for the promotion of tumor cell activation, growth, and survival in HIV-related Hodgkin's lymphoma [80] .

Cervical cancer

Although cervical cancer is designated as an AIDS-defining tumor, an increase in risk with AIDS has not been shown convincingly [10] . A five-fold RR in women with AIDS was observed in the AIDS/Cancer Match Registry Study [10] , but the risk did not increase with time since HIV infection. The RR for invasive cervical cancer 4 to 27 months' post-AIDS onset was 5.4 and for 28 to 60 months' post-AIDS onset was 5.1. Analysis of a subset of women who had CD4 counts at AIDS onset failed to demonstrate an increase in risk as CD4 counts fell [10] . An increased risk for cervical cancer in HIV-infected women would be expected because they have a higher prevalence of persistent infection with high-risk human papillomavirus (HPV) types (eg, HPV 16 and 18) [59] [81] .

Although data on invasive cervical cancer remain inconclusive, cervical intraepithelial neoplasia (CIN) does appear to be increased in late-stage HIV infection. Multiple studies [82] [83] have found greater prevalence and incidence of CIN among HIV-infected women, and an inverse association with CD4 counts [83] . These studies, however, typically have not provided data on the progression of CIN lesions to invasive cervical cancer, because women with CIN are normally treated for this abnormality and do not progress cervical cancers.

In the Women's Interagency HIV Study [82] , cervical cytology was abnormal in 38.3% of 1713 HIV-positive women compared with 16.2% of 482 high-risk, HIV-negative control women. High-grade lesions, low-grade lesions, and atypical squamous cells of undetermined significance all were significantly more common among HIV-infected women [82] . CD4 cell count lower than 200 per cubic millimeter (odds ratio [OR] = 2.13, 95% confidence ratio [CI] = 1.45–3.13) was associated significantly with abnormal cytology.

In the AIDS Link to Intravenous Drug Experience (ALIVE) study [84] , the baseline prevalence of cervical abnormalities was 13.4% among 184 HIV-positive women compared with 2.4% among 84

HIV-negative women [84] . During follow-up, incident CIN was identified in 11 out of 70 (15.7%) HIV-positive women (median CD4 cell counts of 253 per cubic millimeter) compared with 0 out of 37 HIV-negative women who had colposcopies. In a study of 251 commercial sex workers in Thailand [85] , high-grade CIN was more common in women dually infected with HPV and HIV (3 out of 10) compared with women with HPV alone (5 out of 31). In another study of urban high-risk women in the United States [83] , the annual incidence of CIN was 8.3% among 328 HIV-positive women compared with 1.8% among 325 HIV-negative women.

In summary, substantial data indicate that the prevalence and severity of CIN are associated with HIV infection and HIV-related immunodeficiency [86] . Nevertheless, shared routes of transmission and behavioral risk factors for HIV and HPV may confound these associations. An additional complicating factor could be possible impediments to access to cervical Pap smear-screening programs [87] . On the other hand, a higher likelihood for women with HIV infection to be screened for cervical disease could potentially obscure a true association with AIDS (but see discussion of associations in the absence of routine cervical screening, below).

Other anogenital HPV-related cancers

Other anogenital cancers (anus, vulva, vagina, and penis) are somewhat more strongly related to AIDS. In an analysis of the AIDS/Cancer Match Registry Study [10] that focused on HPV-related cancers, the RR for invasive anal cancer was elevated 6.8-fold in women and 37.9-fold in men. The RR for penile cancer was 3.7 and for vulvovaginal cancer was 5.8. Importantly, the risks for penile cancer and in-situ vulvovaginal cancer increased with time since HIV infection [10] . In this study [10] , the incidence of anal intraepithelial neoplasia also increased with declining CD4 counts, indicating a role for immune competence in the control of preneoplastic lesions at these sites. These associations may be due to a failure to clear HPV infection in more severe immunosuppression, as low-grade intraepithelial lesions progress to high-grade lesions through the synergistic actions of the HPV oncoproteins E6 and E7 [88] . Anal cancer already was elevated in homosexual men before the onset of the HIV epidemic, due to patterns of sexual behavior that predated the HIV epidemic. Thus, the additional rise in incidence during the AIDS epidemic may reflect a pre-existing prevalence of high-risk HPV types in people at increased risk for HIV infection.

Leiomyosarcomas

Leiomyosarcomas are extremely rare tumors that have been reported with increased frequency in AIDS, primarily in children. Because pediatric AIDS accounts for less than 1% of the AIDS epidemic, these tumors appear to be associated specifically with childhood AIDS [89] [90] . After NHL, leiomyosarcoma is the second leading cancer in children with HIV infection [89] [90] . A RR of greater than 1900 was reported by Biggar et al [91] based on four cases in data from an AIDS-cancer registry versus none expected; all the cases occurred in the distant post-AIDS period, implying that profound immunosuppression is necessary for the tumors to develop. EBV has been detected in the tumor cells, which may represent a pathogenetic mechanism for the tumor in immunosuppressed children [92] . The RR among adults is much lower at 2.3, and does not increase with relative time since HIV infection [11] .

Testicular cancers

A twofold increase in testicular seminoma among people with AIDS compared with the US general population was reported in the AIDS/Cancer Match Registry Study [11] , whereas risk for nonseminoma testicular cancer was not elevated. Evidence for this association is variable in other studies, however, and the observed association may be coincidental, given the relatively young population at risk for both

AIDS and testicular cancer.

Liver cancer

Whether risk for liver cancer is elevated in people with AIDS has not been determined. An association with HIV/AIDS would be predicted from the shared transmission routes for HIV and hepatitis B and C viruses [11] [78] [93] . HIV infection increases the rate of progression to cirrhosis, but progression to liver cancer does not seem to be affected. Linkage studies have demonstrated a 7-fold increase in the RR of liver cancer during the period before AIDS diagnosis and a 3.3-fold increase in the early post-AIDS period [11] , but the observed risk did not increase with time since HIV infection. The long latency between infection with hepatitis viruses and the development of liver cancer may partially explain the apparent lack of association of liver cancer with AIDS, and an association may emerge as people live longer with both infections because of HAART.

Lung cancer

Lung cancer is the most commonly diagnosed non–AIDS-defining malignancy in people with AIDS. A 4.5-fold increase has been described in people with AIDS in the United States, based on AIDS and cancer registry linkage studies [11] . Lung cancer risk appeared to increase with duration of HIV infection [11] . Similarly, a sixfold increase in risk was reported in an Italian cohort of HIV-infected people [11] [94] . These studies may not have adjusted adequately for the effect of smoking, however, which may be more prevalent among people with HIV infection than in the general population. Therefore, the association of HIV with lung cancer may be spurious.

The AIDS epidemic and cancer risk in sub-Saharan Africa

Less is known about the risk of AIDS-associated cancers in Africa, despite this region being home to two thirds of the HIV-infected population worldwide [95] . The Joint United Nations Program on HIV/AIDS (UNAIDS) has estimated that 29 million people in sub-Saharan Africa were infected with HIV in 2001, and that this number would increase to 55 million by 2020 [95] . Accordingly, even a modest HIV effect on cancer risk could greatly increase cancer incidence [96] . Clinical reports, case-control studies [97] [98] , and registry studies [99] indicate increases in KS and conjunctival cancer related to the AIDS epidemic [100] , but the changes in NHL and cervical cancer are less clear. It appears that the effects of HIV on cancer incidence may vary in magnitude and type between western countries and Africa [101] .

Endemic KS was common in central and eastern Africa even before the AIDS epidemic, but AIDS-related KS has become the most frequent tumor in several African countries [102] [103] [104] . In Uganda–one of the first countries to report AIDS–KS is the most common tumor in men and the second most common tumor in women. Their age-standardized incidence rates rose from 3.2 and 0.1 per 100,000, respectively, in the period from 1960 to 1966 to 39.3 and 21.8, respectively, in the period from 1995 to 1997 (Fig. 4) [102] . Among children, KS accounted for 2% of tumors in the 1960s and 33% in the 1990s. Among adults, the male to female incidence ratio has declined from 20 to 1 to 2 to 1. These gender differences in KS risk do not seem to be explained by differential risk for HHV-8 infection, because HHV-8 seroprevalence is similar in men and women [105] . A protective effect of female hormonal factors has been hypothesized, but aggressive KS tumors can occur in pregnant women [106] [107] . Among HIV-infected people, KS is associated with higher social economic status, history of sexually transmitted diseases [108] , and a higher number of sexual partners [98] . Due to higher KS incidence in the general population, the RR associated with HIV infection is much lower in Africa than in the United States (Table 2) .

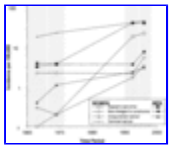

Fig. 4. Incidence of selected cancers in Kyadondo County, Uganda [102] .

Table 2. Associations between HIV and selected cancers from several studies conducted in Africa

Tumor	Country	No. cases (% HIV+)	No. controls (% HIV+)	Odds ratio (95% confidence interval)	References
Kaposi's sarcoma					
Children	Uganda	36 (81)	190 (6.0)	94.9 (28.5–315.3)	Newton et al [97]
Adults	South Africa	112 (79.5)	844 (8.8)	21.9 (12.5–38.6)	Sitas et al [110]
	Rwanda	18 (61.1)	200 (4)	35.0 (8.2–206.7)	Newton et al [109]
Non-Hodgkin's lymphoma					
Children	Uganda	33 (30.3)	190 (6.0)	7.5 (2.8–20.1)	Newton et al [97]
Adults	Uganda	21 (61.9)	112 (21.4)	6.2 (1.9–19.9)	Newton et al [97]
	Uganda	38 (34.2)	124 (20.2)	2.2 (0.9–5.1)	Parkin et al [101]
	South Africa	105 (21.9)	844 (8.8)	5.0 (2.7–9.5)	Sitas et al [110]
	Rwanda	19 (36.8)	200 (4)	12.6 (2.2–54.4)	Newton et al [109]
Cervical cancer	Uganda	65 (32.3)	112 (21.4)	1.6 (0.7–3.6)	Newton et al [97]
	South Africa	1323 (12.6)	556 (9.0)	1.6 (1.1–2.3)	Sitas et al [110]
Conjunctival cancer	Uganda	56 (69.6)	819 (14.5)	10.1 (5.2–19.4)	Newton et al [126] [129]

Data on NHL incidence in Africa are sparse, but three studies have estimated the RR of NHL in HIV-positive people. In Rwanda, Newton et al [109] found an OR of 12.6 (95% = CI 2.2–54.4) based on 19 cases (including cases that were diagnosed only clinically). In South Africa, Sitas et al [110] compared NHL cases with hospital controls who had cancers unrelated to HIV (in men) or vascular disease (in women). Based on 105 NHL cases (all histologically confirmed), they reported an OR of 5.0 (95% CI = 2.7–9.5) [110] . A similar study in Uganda [101] , however, found an OR of 2.2 (95% CI = 0.9–5.1), based on 38 histologically confirmed cases (Table 2) .

Otieno et al [111] identified 29 cases of adult (age 16+) Burkitt's lymphoma from hospitals throughout Kenya in the period from 1992 to 1996, which was considered to be three times the number expected

based on previous incidence rates. Two-thirds (19) of the cases were HIV positive and had a median age of 35 years (typical of patients with AIDS in Kenya), rather than the 16 to 25 years of age of the HIV-negative patients. The HIV-positive cases presented with diffuse lymph node involvement, in contrast to the HIV-negative cases, who had typical endemic Burkitt's lymphoma with complete sparing of peripheral lymph nodes. Lucas et al [112] found NHL at autopsy in 2.8% of HIV-positive decedents in Côte d'Ivoire, which was somewhat lower than the cumulative probability of lymphoma for AIDS patients in the United States [113] . These studies suggest a lower risk for NHL in African patients with AIDS, which may reflect competing mortality from conditions that are common even in patients without AIDS [114] . The reported median survival of 10 years from HIV seroconversion, however, was similar to the survival that was observed in Western countries before effective antiretroviral drugs were introduced [115] . The level of immune dysfunction at AIDS diagnosis—as measured by CD4+ counts—was less severe in African AIDS patients than in AIDS patients from Western countries, and the median survival after AIDS diagnosis was shorter [116] . Thus, patients in Africa may have a relatively shorter duration of immune suppression and consequently a shorter time at risk for NHL.

NHL incidence in Africa is increasing. In Uganda, NHL incidence increased threefold in the past 4 decades, from 2.3 per 100,000 in the period from 1961 to 1971 to 6.6 in 1997 (Fig. 4) [102] . Most of the increases were due to pediatric Burkitt's lymphoma (from 0.9 to 3.8 for the two time periods) and to diffuse large B-cell lymphoma in young adults. The proportion of the increase attributable to AIDS is not known, however, and other factors such as improved access to medical care, better case ascertainment, or temporal trends unrelated to HIV may have contributed.

Changes in the incidence of cervical cancer during the AIDS epidemic are even less clear. Case-control studies have failed to demonstrate an excess risk of invasive cancer in HIV-infected women [97] [110] . In a recent study from Johannesburg [110] , the prevalence of HIV among 1323 cases of cervical cancer was 12.6% versus 9.0% in a comparison group of hospital patients with a mixture of non-HIV-related cancers or vascular disease (OR = 1.6, 95% CI = 1.1–2.3). Newton et al [97] observed a nonsignificantly higher HIV prevalence of 32% in 65 women with cervical cancer in Kampala, Uganda, compared with 21% in 112 controls with nonrelated cancers or noncancerous conditions (OR = 1.6, 95% CI = 0.7–3.6) (Table 2) . The lack of a clear effect of HIV on the risk of invasive cancer may be due to competing causes of mortality in HIV-infected women.

In a study of 4058 women who were attending family planning clinics in Nairobi, Kenya, Maggwa et al [117] found CIN in 4.9% of HIV-positive women compared with 1.9% in women who were HIV negative (adjusted OR = 2.78, 95% CI = 1.32–5.85). In another study of 2198 women who were attending gynecology clinics in Abidjan, Côte d'Ivoire, La Ruche et al [118] [119] observed that HIV-positive women had a significantly higher prevalence of squamous intraepithelial lesions (SIL), with ORs of 3.6 for low-grade SIL and 5.8 for high-grade SIL. The risk of low-grade SIL was inversely associated with CD4+ count. Kapiga et al [120] also found that the risk of SIL among 691 HIV-positive women in Dar es Salaam, Tanzania, was higher among those with a CD4+ cell count below 200 per microliter. In Kigali Rwanda, Leroy et al [121] found a significantly higher prevalence of SIL in 103 HIV-positive pregnant women who were attending antenatal clinics than in 107 HIV-negative gravida (OR = 4.6, 95% CI = 1.8–12.3), but the risk among the HIV-seropositive women was not associated with degree of immunosuppression. In contrast, no association between HPV and HIV was apparent in two studies in Kenya and Tanzania [122] [123] . In their study of Nairobi prostitutes, Kreiss et al [122] found that HIV infection was associated with only a modest and nonsignificant increase in the prevalence of HPV infection (37% versus 24% in HIV-unifected subjects; OR = 1.7). In women who were attending an antenatal clinic in Mwanza, Tanzania, the OR for the association of HPV infection with HIV was 1.02 (95% CI = 0.6–1.6) [123] . Because of the shared routes of transmission for HPV and HIV infections, it is not surprising that in some studies, CIN or SIL is more prevalent in HIV-positive than in HIV-negative women. The incidence of cervical cancer in the general population has increased only modestly (Fig. 4) ,

which could be accounted for by rural–urban migration and better access to medical care. Because African countries have not implemented cervical Pap smear screening programs yet, the lack of an increase in cervical cancer despite a high prevalence of HIV infection belies the hypothesis that cervical screening has obscured an association between AIDS and cervical cancer in Western countries [124] . Carefully designed studies need to address the paradox of an apparent association between HIV and high-grade SIL in the absence of an association with invasive disease.

Squamous cell carcinoma of the conjunctiva, which is rare in Western countries, is associated with AIDS in Africa. The association with HIV was reported first by Ateenyi-Agaba [100] , who observed that 75% of patients with conjunctival tumors who were seen at Mulago Hospital were HIV seropositive compared with 19% of cases with nonmalignant eye conditions. Several case-control studies [125] have replicated these findings [126] . A rise in the incidence of eye tumors also was noted in the general population of Kyadondo County, Uganda, from about 0.2 per 100,000 in 1960 to 1966 to 3.0 in 1995 to 1997, with the proportion due to squamous conjunctival cancer increasing over this period from 23.5% to 71% in men and 0% to 85% in women [102] . The cause of this tumor is not known, but correlation with ambient ultraviolet light may explain its higher incidence in equatorial Africa. An apparent association with HPV also hs been reported [127] .

Liver cancer was the most common cancer in men in Africa before the AIDS epidemic, but its incidence has not increased during the AIDS epidemic. In Africa, liver cancer may be underascertained because of limited access to diagnostic services. In addition, the poor prognosis associated with liver disease may be a further barrier to evaluation of patients who are suspected of having liver cancer. Nonetheless, the high prevalences of chronic hepatitis B infection, hepatitis C infection, and HIV infection in many African countries provide a large co-infected population in whom the impact of HIV infection on liver cancer may be monitored [128] [129] . Because liver cancer has a long induction period, it may be premature to come to any conclusions about its association with HIV.

Future prospects

Two decades after the discovery of HIV as the cause of AIDS, it is now clear that this virus is not a sufficient cause of cancer. Instead, HIV infection increases cancer risk for a limited set of cancers, some of which are associated with other viral infections. This selective increase in risk may be mediated, in part, by uncontrolled proliferation of oncogenic viruses as immunosuppression worsens. There is no demonstrable increase in incidence of the most common epithelial cancers in people with AIDS, but the long-term impact of HIV infection is not known. As people with HIV infection live longer with mild disturbances in immune competence, new associations may become apparent. Although the introduction of HAART has reduced the risk for AIDS-associated cancers in Western countries, less than 1% of AIDS patients in sub-Saharan Africa are receiving these life-saving drugs. Given the magnitude of the AIDS epidemic and its continued expansion into new regions of the world, the impacts on cancer risk are likely to continue for a long time and touch many people.

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